The Toxicology of Cefuroxime

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The results of routine toxicity tests showed cefuroxime to have very low toxicity. Detailed results will be published elsewhere. The acute intravenous LD_{50} for mice was greater than 10 g/kg. In single dose tolerance tests, mice were given 10 g/kg intravenously (i.v.) or subcutaneously (s.c.); rats were given 4 g/kg i.v. or 5 g/kg s.c. and cats, dogs and monkeys (*Macaca fascicularis*) were given 2 g/kg by the intramuscular (i.m.) route. These animals were observed for 4–7 days and then killed for histological examination. In general the doses were well tolerated. There was moderate local irritation in all species, soft fæces were noted in rats dosed i.v. and in monkeys and one rat dosed i.v. died immediately after injection.

In subacute tests, rats were given 100–400 mg/kg/day i.v. daily for 4 weeks, 100–900 mg/kg/day s.c. for 13 weeks, followed by 3 weeks without dosing and 50–450 mg/kg/day s.c. for 26 weeks. Monkeys (*M. fascicularis*) were given 150 or 450 mg/kg/day i.m. for 4 weeks and dogs were given 50 mg/kg/day i.m. or 150 or 450 mg/kg/day s.c. for 26 weeks. Observations on the animals included general health and body weight, extensive analyses of blood and urine during treatment, and detailed histological examination of tissues at termination. In the test on monkeys, special investigations were made to detect any hepatotoxic effect. These included measurement of additional serum enzymes and electron microscopy of liver sections.

Treatment had no detectable effect on rats dosed i.v. and no more than minor effects in the other experiments. There was usually some local reaction to i.m. or s.c. injections, which may have contributed to the slight reductions of erythrocyte indices observed. Rats were most affected. Hæmoglobin, for example, was reduced to 87% of the control concentration in those given 900 mg/kg/day, although this resolved soon after dosing ceased. Rats given very large doses showed a slight reduction of serum albumin and calcium, occasional slight reductions of serum alanine transaminase activity and increased urine volume and urine electrolyte output. In rats dosed for 26 weeks there was an age-related nephropathy. The incidence, though not the severity, was slightly greater in antibiotic treated rats, irrespective of dose. A transient neutrophilia and eosinophilia was seen in some of the treated monkeys, but there were no other treatment related changes in any of the species tested.

Fertility, organogenesis and perinatal studies were carried out in mice or rabbits. In fertility tests, mice of each sex were given s.c. doses of up to 3200 mg cefuroxime/kg/day for 60 days before mating and treatment of the females was continued up to day 17 or 18 of pregnancy. Half the females were killed at this stage for examination of the foetal skeletons and soft tissues and the remainder were allowed to rear their young. Some of the latter were mated to produce another generation.

In the organogenesis test, mice were given up to 6400 mg/kg/day s.c. on days 6 to 15 of pregnancy and rabbits up to 400 mg/kg/day i.m. on days 6 to 18. The fœtuses were removed for examination just before parturition.

In the perinatal studies, mice were given up to 3200 mg/kg/day s.c. from day 16 of pregnancy until weaning, and rabbits up to 200 mg/kg/day i.m. from day 19 of pregnancy until weaning. The effects on parturition, on weaning and on development of the young were observed. Cefuroxime had no adverse effects in any of these tests of reproduction.

Transient increases of serum transaminases have been reported in a small proportion of patients (Norrby *et al.* 1977) and although our routine toxicity tests and special studies in monkeys positively excluded any significant effect on the liver or kidneys, we have performed a hepatotoxicity test in dogs aimed at detecting any transient changes. Also, because all cephalosporins are suspected to be nephrotoxic, we have completed a series of nephrotoxicity tests, including tests in rats based on the clinical situations in which renal failure is most frequently reported in association with cephalosporin therapy (Foord 1970, 1975). These are excessive dosage, the concurrent administration of frusemide or an aminoglycoside and the existence of renal impairment. The model for producing renal impairment in rats is based on that described by Linton *et al.* (1972) and Lawson *et al.* (1972).

METHODS

Drugs

Cefuroxime sodium, cephaloridine (Ceporin, Glaxo Laboratories Ltd), frusemide (Lasix Injection, Hoechst UK Ltd), glycerol (AnalaR grade, BDH Chemicals Ltd), gentamicin sulphate (Genticin Pure Powder, Nicholas Laboratories Ltd), amikacin sulphate (Amikin Injection, Mead Johnson Laboratories) and tobramycin sulphate (Nebcin, Eli Lilly and Co Ltd) were administered as aqueous solutions or suspensions by the s.c. route to mice, rats and dogs and by the i.m. route to rabbits. Doses of cefuroxime are expressed in terms of the sodium salt, frusemide as the acid and the aminoglycosides as the base.

Animals

Mice were females of the CRH strain weighing 16–20 g and rats were males of the Charles River CD strain weighing 225–360 g. The rabbits were females of the New Zealand White strain weighing 2.2–2.7 kg and the dogs were pure-bred beagles, 7–12 months old. All were housed in controlled environments and provided with an appropriate standard diet and drinking water *ad libitum*.

Hepatotoxicity

Groups of 3 male dogs were given cefuroxime by s.c. injection once daily for 10 days at dosages of 100 or 300 mg/kg/day. Similar groups were given the same dosages as three divided doses each day, at intervals of 8 h. Maximum serum concentrations after the first dose on day 0 (the first day of treatment) and day 7 ranged from 30 to 150 mg cefuroxime/litre according to dosage.

Serum enzyme activities were measured on 3 occasions before the start of treatment: also on day 0 and day 7 at 1, 4 and 8 h after the first dose, and on days 0, 1 and 9 at 24 h after the first dose. The enzymes measured were alkaline phosphatase (ALP), alanine transaminase (ALT), sorbitol dehydrogenase (SD), glutamate dehydrogenase (GD) and aspartate transaminase (AST). The results were subjected to analyses of variance to calculate the contribution of treatment (total daily dose), dosage regimen (once or three times daily) and the interaction between treatment and dosage regimen. At the end of treatment the dogs were killed and hæmatoxylin and eosin stained sections of the liver were examined microscopically.

Nephrotoxicity

In nephrotoxicity tests the kidneys were examined histologically 48 h after a single dose or 24 h after the last of the repeated doses. A median transverse section of the right kidney, stained with hæmatoxylin and eosin, was routinely examined. Acute tubular necrosis, selected as a quantitative endpoint, was confined to proximal tubules located in the inner or outer cortical zones, according to treatment and the proportion of necrotic tubules was estimated visually. When appropriate, less severe changes were also assessed.

Urine was collected in an open glass vessel at ambient temperature from rats housed individually for 16 h overnight without food but with water *ad libitum*. The urine was weighed and a sample centrifuged. The supernatant was stored at 0–4°C and all measurements on it were completed within 8 h of the end of the collection period. Urine protein was assayed by a standard turbidimetric method and urine alkaline phosphatase (ALP), lactate dehydrogenase (LD), γ-glutamyl transpeptidase (γGT) and leucine aminopeptidase (LAP) activities were assayed by standard kinetic methods without dialysis. The statistical significance of differences between group means was calculated by Dunnett's t test (Dunnett 1955).

Mice: In the first of two experiments mice were given a single dose of cefuroxime (10 g/kg) or cephaloridine (1.1 g/kg) either alone or with frusemide (50 mg/kg). In the second experiment glycerol (5.4 ml/kg, sufficient to produce tubular necrosis in most mice) was given at the same time as cefuroxime and frusemide and blood urea nitrogen (BUN) was measured at termination.

Rats: Seven experiments were carried out.

(1) Rats were given single doses of cefuroxime (2, 4, 6, 8 or 10 g/kg). Urine output, urine protein and urine enzyme activities were measured in samples collected during the periods 8–24 and 32–48 h after injection, and blood urea nitrogen was measured at termination.

(2) Rats were given 5 g cefuroxime/kg/day once daily for 10 consecutive days. Urine output, urine protein and urine enzyme activities were measured in samples collected overnight after every dose except the sixth and seventh. Blood urea nitrogen was measured at termination.

(3) Rats were given single doses of cefuroxime (2, 4 or 6 g/kg) either alone or with frusemide (100 mg/kg, the minimum dose found to produce maximal diuretic effect).

(4) Rats were given single doses of cefuroxime (0.5, 1, 2 or 4 g/kg) in combination with frusemide (100 mg/kg) and glycerol (2 ml/kg, sufficient to cause tubular necrosis in most rats).

(5) Rats were given gentamicin (35 mg/kg/day, sufficient to cause tubular necrosis in most rats) once daily for 10 consecutive days and a single dose of cefuroxime (2, 4 or 6 g/kg) with the ninth dose.

(6) Rats were given both gentamicin (35 mg/kg/day) and cefuroxime (0.5, 1 or 2 g/kg/day) once daily for 10 consecutive days.

Table 1

The effect of frusemide on the nephrotoxicity to mice of single doses of cefuroxime or cephaloridine

		Acute tubular necrosis at 48 h	
Drugs administered	*Dose/kg*	*Proportion of mice affected*	*Extent (mean %)*
None		0/9	
Frusemide	50 mg	0/9	
Cefuroxime	10 g	0/9	
Cefuroxime + Frusemide	10 g 50 mg	2/9	< 1
Cephaloridine	1.1 g	5/9	7
Cephaloridine + Frusemide	1.1 g 50 mg	8/9	16

Table 2

Nephrotoxicity of a single dose of cefuroxime alone or with frusemide to normal or glycerol treated mice

Drugs administered	*Dose/kg*	*No. mice per group*	*BUN at 48 h (mmol/l)*	*Acute tubular necrosis at 48 h*	
				Proportion of mice affected	*Extent (mean %)*
None		8	19.5	0/8	
Frusemide +Glycerol	50 mg 5.4 ml	8	17.2	4/8	6
Cefuroxime	10 g	7	21.5	0/7	
Cefuroxime +Frusemide	10 g 50 mg	8	16.1	0/8	
Cefuroxime +Glycerol	10 g 5.4 ml	8	17.0	5/8	2
Cefuroxime +Frusemide +Glycerol	10 g 50 mg 5.4 ml	8	19.3	3/8	7

Table 3

Nephrotoxicity of a single dose of cefuroxime to rats

Observation	*Time after dosing (h)*	*Dose of cefuroxime (g/kg)*					
		0	*2*	*4*	*6*	*8*	*10*
Acute tubular necrosis:							
proportion of rats affected	48	0/5	0/5	3/5	5/5	5/5	5/5
extent (mean %)	48			9	17	30	39
Blood urea nitrogen (mmol/l)	48	5.0	6.2	9.1	14.5	20.8[a]	26.9[a]
Urine weight (g)	8–24	16	34	50[a]	45[a]	34	37
	32–48	8	10	23	30	23	35[a]
Urine output:							
protein (mg)	8–24	1.7	1.4	10.1	18.2	36.7[a]	23.3[a]
	32–48	1.0	1.0	8.3	26.8[a]	26.5[a]	25.9[a]
alkaline phosphatase (iu)	8–24	1.9	1.7	6.1	9.4	30.2a	21.8
	32–48	1.1	4.2	14.3	19.7[a]	18.9[a]	25.0[a]
lactate dehydrogenase (iu)	8–24	0.06	0.1	2.0	4.4	6.2	6.5
	32–48	0.05	0.28	5.4	13.6[a]	14.5[a]	15.6[a]
γ-glutamyl transpeptidase (iu)	8–24	11	11	37	59	116[a]	73
	32–48	14	25	57	83[a]	66	98[a]

a = group significantly different from control ($P < 0.05$)

(7) Rats were given tobramycin (60 mg/kg/day) or amikacin (250 mg/kg/day) in combination with cefuroxime (2 or 4 g/kg/day) once daily for 10 consecutive days.

Rabbits: Six rabbits were given single doses of cefuroxime (0.2 g/kg) and 2 were given single doses of cephaloridine (0.14 g/kg).

RESULTS

Hepatotoxicity

Cefuroxime had no effects on serum enzymes or liver histology in dogs given up to 300 mg/kg/day as a single or as 3 divided doses daily for 10 days.

Nephrotoxicity

Single doses of cefuroxime in mice: Cefuroxime alone did not cause necrosis at a dose of 10 g/kg. In the first experiment (Table 1) this dosage produced a small amount of necrosis in a small proportion of mice when given in combination with frusemide, but this result was not reproduced in the second experiment (Table 2). Glycerol-induced damage was not affected by cefuroxime, whether or not frusemide was given concurrently.

Single doses of cefuroxime in rats (Table 3): All the indicators of renal damage were clearly, if not significantly, affected at a dose of 4 g/kg, with more marked changes at larger doses. At 2 g/kg there was no frank tubular necrosis; isolated necrotic cells were observed, indicating some increase in turnover of the tubular epithelium, and there were minimal increases in output of ALP, LD and γGT.

Ten daily doses of cefuroxime in rats (Fig 1): During treatment with 5 g/kg/day, mean results

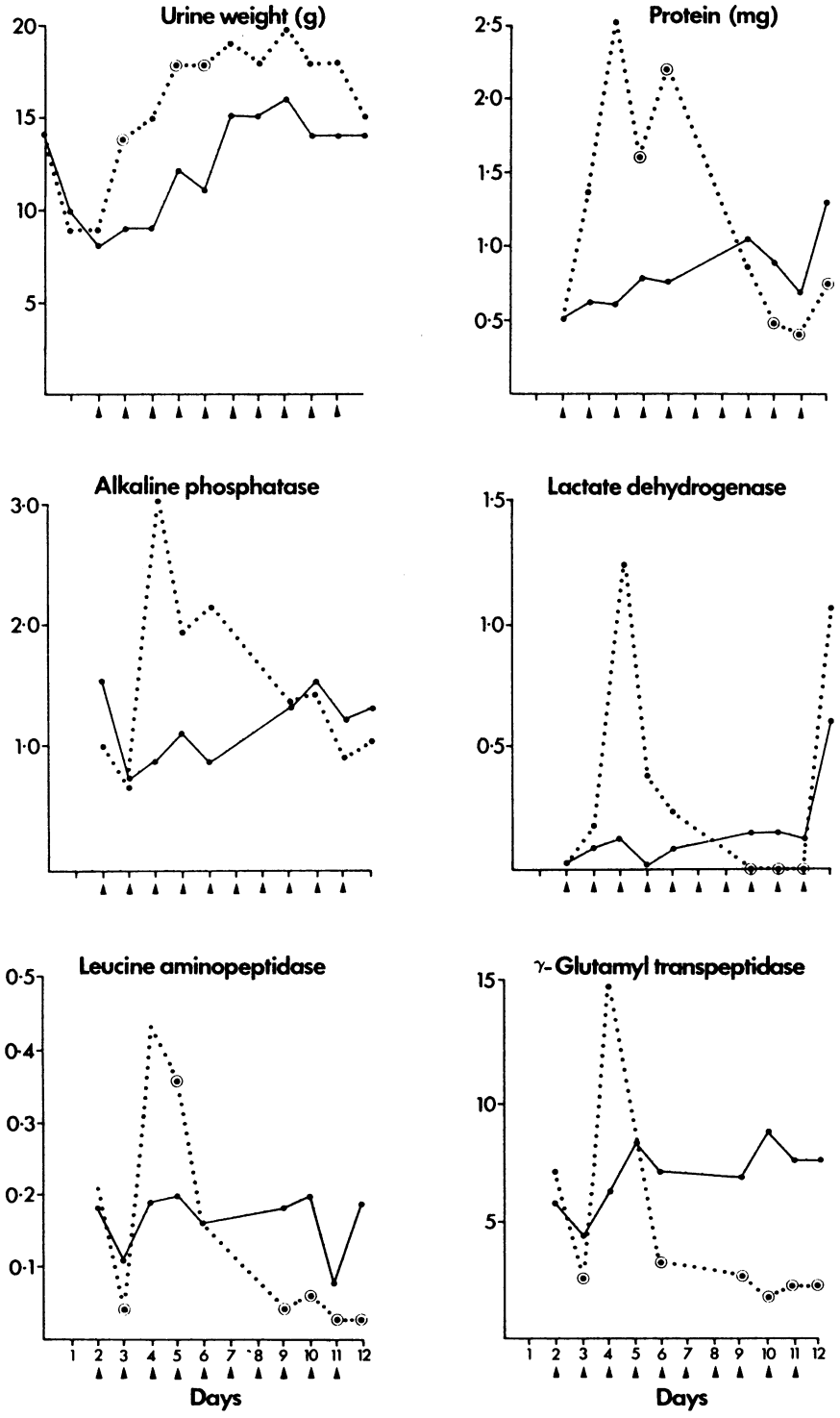

Fig 1 *Urine weight and protein and enzyme output from rats given 5 g cefuroxime/kg/day for 10 days (. . . . .) compared with controls (——·). Doses are indicated by arrow heads ▲ and encircled results are significantly different from controls ($P<0.05$); 10 rats in each group.*

for urinary indicators of renal damage showed marked effects by the second day, followed by an improvement. After the seventh and subsequent doses, urine weight and output of ALP were similar to controls and the urine outputs of protein, LD, γGT and LAP were less than controls. By termination, blood urea nitrogen and kidney histology were normal, though the general condition of the animals and their body weight gain during the observation period was inferior to controls.

Cefuroxime and frusemide in rats (Table 4): There was no tubular necrosis with a dose of 2 g cefuroxime/kg, but frusemide enhanced the effect of 4 or 6 g cefuroxime/kg.

Cefuroxime and frusemide in glycerol-treated rats (Table 5): A dose of 0.5 g cefuroxime/kg did not affect the amount of cortical tubular necrosis in rats treated with glycerol and frusemide but 1 g/kg or more enhanced it. The necrosis produced by glycerol and frusemide primarily affected the proximal tubules in the outer renal cortex, whereas cefuroxime alone primarily affected those in the inner cortex. In this experiment 2 g cefuroxime/kg produced inner cortical damage in rats treated with glycerol and frusemide and at 4 g/kg the extent of damage was enhanced.

Cefuroxime and aminoglycosides: The results of the administration of cefuroxime as a single dose with the ninth of 10 daily doses of gentamicin are given in Table 6. Gentamicin produced a consistent amount of renal damage, mainly necrosis of proximal tubules in the outer cortex, whether or not cefuroxime was given. Tubular necrosis in the inner cortex was absent in the gentamicin-treated rats given cefuroxime at 2 g/kg and the extent of inner cortical necrosis in rats given 4 or 6 g/kg was similar whether or not gentamicin was given.

When cefuroxime was given concurrently throughout 10 days of treatment with gentamicin, tobramycin or amikacin (Table 7) the nephrotoxic effects of the aminoglycosides were alleviated. As there was little tubular necrosis, an assessment of other histological changes is also tabulated. These included vacuolation of epithelial cells, tubular dilatation, debris in tubules, mild chronic interstitial inflammation and evidence of regeneration.

Single doses of cefuroxime in rabbits: Cefuroxime caused no kidney damage at a dose of 0.2 g/kg, whereas cephaloridine 0.14 g/kg produced extensive tubular necrosis. Larger doses of cefuroxime were not given to rabbits because of their susceptibility to antibiotic-induced gastrointestinal disturbance.

Table 4

The effect of frusemide on the nephrotoxicity to rats of single doses of cefuroxime

		Acute tubular necrosis at 48 h	
Drugs administered	*Dose/kg*	*Proportion of rats affected*	*Extent (mean %)*
None		0/5	
Frusemide	100 mg	0/5	
Cefuroxime	2 g	0/5	
Cefuroxime	4 g	3/5	5
Cefuroxime	6 g	4/5	9
Cefuroxime + Frusemide	2 g 100 mg	0/5	
Cefuroxime + Frusemide	4 g 100 mg	4/5	8
Cefuroxime + Frusemide	6 g 100 mg	5/5	30

Table 5

Nephrotoxicity of single doses of cefuroxime with frusemide in glycerol treated rates

		Acute tubular necrosis at 48 h	
Drugs administered	*Dose/kg*	*Proportion of rats affected*	*Extent (mean %)*
None		0/5	
Frusemide + Glycerol	100 mg 2 ml	3/5	1
Cefuroxime + Frusemide + Glycerol	0.5 g 100 mg 2 ml	2/5	2
Cefuroxime + Frusemide + Glycerol	1 g 100 mg 2 ml	5/5	20
Cefuroxime + Frusemide + Glycerol	2 g 100 mg 2 ml	5/5	31
Cefuroxime + Frusemide + Glycerol	4 g 100 mg 2 ml	5/5	66
Cefuroxime	4 g	2/5	8

Discussion

Routine toxicological examination has demonstrated excellent tolerance of a single and repeated

Table 6

Nephrotoxicity to rats of a single dose of cefuroxime given on the ninth day of 10 successive days of gentamicin treatment

		Acute tubular necrosis on day 11	
Drugs administered	*Dose/kg*	*Proportion of rats affected*	*Extent (mean %)*
None		0/6	
Gentamicin	35 mg	5/6	20
Cefuroxime	2 g	0/6	
Cefuroxime	4 g	3/6	5
Cefuroxime	6 g	6/6	13
Gentamicin + Cefuroxime	35 mg 2 g	6/6	15
Gentamicin + Cefuroxime	35 mg 4 g	6/6	26
Gentamicin + Cefuroxime	35 mg 6 g	6/6	34

Table 7

Nephrotoxicity to rats after 10 days of treatment with cefuroxime, combined with gentamicin or tobramycin or amikacin

Drugs administered	*Dose/kg/day*	*Acute tubular necrosis on day 11*		*Other histological changes (see text)*
		Proportion of rats affected	*Extent (mean %)*	
None		0/6		—
Cefuroxime	0.5 g	0/6		—
Cefuroxime	1 g	0/6		—
Cefuroxime	2 g	0/5		—
Gentamicin	35 mg	3/6	2	+++
Gentamicin 35 mg + Cefuroxime	0.5 g	2/6	< 1	++
Gentamicin 35 mg + Cefuroxime	1 g	0/6		+
Gentamicin 35 mg + Cefuroxime	2 g	0/6		+
None		0/6		—
Cefuroxime	2 g	0/6		—
Cefuroxime	4 g	0/6		+
Tobramycin	60 mg	4/6	< 1	+++
Tobramycin 60 mg + Cefuroxime	2 g	0/6		+
Tobramycin 60 mg + Cefuroxime	4 g	0/6		++
Amikacin	250 mg	5/6	3	++
Amikacin 250 mg + Cefuroxime	2 g	1/6	< 2	+
Amikacin 250 mg + Cefuroxime	4 g	1/6	< 1	+

doses of cefuroxime by experimental animals and no effects on reproductive function.

No damage to the liver was demonstrable in a previous repeated dose test on monkeys of 4 weeks duration, in which the activities of 6 serum enzymes were measured and electron microscopic examination of the liver was performed. The lack of effect on the liver has now been confirmed by a special test on dogs.

Particular attention to potential nephrotoxicity has shown that clinically relevant dosages are quite safe, with an ample safety margin, in experimental animals. The largest single doses tested in mice and rabbits (10 g/kg and 0.2 g/kg respectively) failed to cause proximal tubular necrosis; 2 g/kg produced only minimal changes in occasional rats. These doses are 4–10 times larger than the corresponding doses of cephaloridine, as judged by the present results and earlier studies in this laboratory (Atkinson, Currie *et al.* 1966). Acute tubular necrosis was produced in rats by single doses of 4 g/kg or more.

Measurements of urinary output of protein or enzymes in rats were good indicators in these experimental conditions of tubular necrosis, but were no better than histological examination. The initial renal damage caused by repeated doses of 5 g/kg/day resolved rapidly and there was no remaining histological abnormality at the end of 10 days of treatment. Similar tolerance occurred with cephaloridine and may be associated with a reduced susceptibility of regenerating epithelium (Atkinson, Caisey *et al.* 1966).

Cefuroxime was slightly more nephrotoxic in mice and rats when frusemide was given concurrently, and this was further enhanced in rats, but not mice, when the kidney was also damaged by glycerol treatment. Similar results have been reported in such a model with cephaloridine, cephalothin and cephacetrile (Dodds & Foord 1970, Linton *et al.* 1972, Lawson *et al.* 1972, Luscombe & Nicholls 1975).

These histological studies in rats incidentally revealed that the aminoglycosides and glycerol with frusemide produce tubular damage primarily in the outer cortex, whereas with cefuroxime it is primarily in the inner cortex. Studies of aminoglycoside combinations with cefuroxime did not reveal any mutual potentiation of renal damage. When given concurrently for 10 days, cefuroxime alleviated the effects of nephrotoxic doses of gentamicin, tobramycin and amikacin. Similar results have been reported with cephalothin (Dellinger *et al.* 1976), cefazolin and cephaloridine (Luft *et al.* 1976) though in the studies by Harrison *et al.* (1975) these 3 cephalosporins were found neither to protect nor to potentiate the effects of gentamicin. These observations do not support the rather tenuous clinical evidence that combined cephalosporin/aminoglycoside therapy is more likely to cause renal damage than either antibiotic used alone (Foord 1970, 1975; Cabanillas *et al.* 1975).

Our studies in animals indicate that cefuroxime will be free from significant adverse effects in man, as has proved to be the case in clinical trials to date.

Summary

Cefuroxime was well tolerated in routine toxicity tests and has now been subjected to specific tests for effects on liver and kidneys. No hepatic changes were detected in dogs given up to 300 mg/kg/day s.c. for 10 days as a single or as three divided doses, which confirmed results in monkeys given up to 450 mg/kg/day i.m. once daily for 4 weeks.

A single dose of 4 g/kg s.c. or more produced tubular necrosis in rats, although at the end of 10 days of repeated dosage with 5 g/kg/day, recovery was complete. Cefuroxime failed to produce renal proximal tubular necrosis at doses up to 10 g/kg s.c. in mice and 0.2 g/kg i.m. in rabbits.

When frusemide was given concurrently, cefuroxime was just nephrotoxic in mice at a dose of 10 g/kg and the effect in rats was enhanced. It was further enhanced by the presence of glycerol-induced renal damage in rats, although not in

mice. Cefuroxime provided some protection against the nephrotoxic effects of gentamicin, tobramycin and amikacin in rats.

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DISCUSSION

Dr R Wise (*Birmingham*) asked Dr Muggleton to expand on the effect of insertion of a 7-methoxy group into the cephalosporin nucleus.

Dr Muggleton said that these were preliminary results, but after examining the effect of a 7-0-methyl group in about 6 cephalosporins, the ratio of transpeptidase activity to MIC was adversely affected. The 7-0-methyl compounds had transpeptidases 5 and 6 as primary targets, and these were believed to be non-lethal targets in Gram negative organisms. This appeared to be an important structure-related observation that should be borne in mind for the future.

Dr M Siegel (*Sacramento*) asked for nephrotoxicity data comparing cefuroxime with cephalothin.

Dr Foord said that studies were not yet complete, but that cefuroxime was significantly less nephrotoxic than cephalothin.

Mr A J Bron (*Oxford*) asked if toxicity studies had been done in conjunction with probenecid.

Dr Foord said that such studies were in progress; in experiments done so far in the rat, probenecid had no effect. This was perhaps not surprising, since in the work originally done with cephaloridine, probenecid had an effect in the mouse but not in the rat. As yet no work has been performed in the mouse with cefuroxime and probenecid.

Mr A J Bron (*Oxford*) asked why different peak serum levels were found after exercise. He wondered whether the kidneys were involved.

Dr O'Callaghan said that the volunteers had been exercising by stepping on and off a box. Thigh muscle particularly was being considerably exercised and she attributed the different peak levels purely to an increased vascular flow taking the material away from the site of injection more quickly.

Dr R Rangoonwala (*Frankfurt*) was interested in the question of renal tolerance with cefuroxime and frusemide. The mice had been given 10 g/kg of cefuroxime. He asked how much frusemide they had received.

Dr Foord said the dose of frusemide in mice had been 50 mg/kg and in rats 100 mg/kg, the minimum dose to produce the maximum diuretic effect.

Dr R Rangoonwala (*Frankfurt*) asked if any experiments had been done in which cefuroxime and aminoglycosides had been given, but not simultaneously. In hospitals generally, cefuroxime was given 3 or 4 times daily and aminoglycosides twice daily. But there was some animal work that suggested that different results would be obtained if the two were not given simultaneously.

Mr Capel-Edwards said that in the work described, they were given at the same time but at different injection sites once a day.

Professor D Hoeffler (*Darmstadt*) asked at what level cefuroxime was likely to be neurotoxic.

Dr Foord said that cefuroxime had not been found to be neurotoxic at any of the doses that were likely to be encountered clinically.

Dr O Ogundipe (*Lagos*) asked whether cefuroxime had any effect on the enzyme glucose-6-phosphate dehydrogenase as, in his country, 20–25% of the population were deficient in this enzyme. He also asked about its effect on the normal bacterial flora in the gastrointestinal tract, and whether it crossed the placental barrier.

Dr Foord said they had no information on the effect of glucose-6-phosphate dehydrogenase. As to bacterial gut flora, there were certainly gastrointestinal disturbances in the rabbit, which was why they had used small doses with this species. However, there was no evidence to suggest an effect on human gastrointestinal flora. On placental transfer, he believed this question would be discussed later.

Dr Labeeuw (*Lyons*) asked if administration of cefuroxime might change the kinetics of gentamicin.

Dr Foord said that they had been concerned to know if cefuroxime would enhance the nephrotoxicity of aminoglycoside antibiotics. He had first suggested that using a cephalosporin/aminoglycoside combination clinically might be more toxic than either alone. However, in animals two other groups had shown the reverse, and one group had shown neither enhancement nor protection. On putting cefuroxime to the test, high dosages were found to protect the rat kidney from the nephrotoxic effect of the aminoglycoside. However, at doses of 1-2 g/kg these results were quite unrealistic in the human context. He did not know whether doses of 20–60 mg/kg/day of cefuroxime would afford any protection against aminoglycoside toxicity in man. Certainly he had no reason to believe that cefuroxime would make the aminoglycoside effect worse; it might even be of benefit.